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REMARKS

Claims 1, 26, 28, and 53 are pending in the present application.

Claims 2-25, 27, and 29-52 have been cancelled without prejudice.

Claim 1 has been amended to delete the phrase "at least" before the phrase "one CCL21".

No new matter is introduced by this amendment.

Prior Rejections.

Applicants gratefully acknowledge that the prior rejections have been withdrawn.

Rejections Under the First Paragraph of 35 U.S.C. §112.

Claims 1, 26, 28, and 53 stand rejected under the first paragraph of 35 U.S.C. §112, as allegedly including new matter. According to the Office Action, there allegedly is no support in the specification for the term "at least one CCL21 cytokine". Applicants point out that the phrase "at least one cytokine" appeared in the original claims, and that only CCL21 (a cytokine) was added by amendment. In the interest of facilitating prosecution, the phrase "at least" has been deleted. The Office Action acknowledges that there is support for inclusion of a single CCL21 cytokine in the vaccine. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. §103(a).

Claim 1 stands rejected as allegedly being obvious under 35 U.S.C. §103(a) over the combination of Rovero *et al.* in view of Gordan *et al.*, Nagira *et al.*, and Lu *et al.* Claim 26 stands rejected over the same references as claim 1 and further in view of Bennet *et al.* Claim 28 stands rejected over the same references as claim 1 and further in view of Tanabe *et al.* Claim 53 stands rejected over the same references as claim 1 and further in view of Bennett *et al.* and Tanabe *et al.* These rejections are unwarranted. A *prima facie* case for obviousness simply has not been established.

According to the Office Action, it would have been obvious to one of ordinary skill in the art to have replaced the DNA encoding Her-2/neu antigen of the Rovero vaccine

with DNA encoding survivin, based on the teachings of Gordan *et al.* (i.e., that survivin is a desirable target for anti-cancer therapy). The Office Action also asserts that one of ordinary skill in the art would have been motivated to replace the IL-1β DNA of the Rovero vaccine with CCL21 DNA, based on the teachings of Nagira *et al.* regarding the immune stimulating ability of CCL21 for attracting B and T cells, and that one of ordinary skill in the art would have been motivated to incorporate the so-modified Rovero vaccine in an attenuated *Salmonella typhimurium* vector based on the teachings of Lu *et al.*

In essence, the Office Action asserts that the *de novo* rebuilding of the Rovero vaccine utilizing survivin DNA and CCL21 DNA in an attenuated *Salmonella typhimurium* vector would have been obvious due to the reported biological properties of the various components. This argument is nothing more than a variant on the "obvious to try" standard, in which the person of ordinary skill in the art is expected to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result. The Supreme Court has indicated that "obvious to try" may amount to "obvious" when there "are a finite number of identified, predictable solutions, [and] a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." See *KSR Int'l Co. v. Teleflex Inc.* 127 S. Ct. 1727 (2007). That is not the case here, however.

The present invention does not represent a *predictable* variation of known elements or techniques in prior arts or fields of endeavor. As acknowledged in the previous Office Action, which rejected the original claims for lack of enablement, the anti-cancer art is relatively unpredictable. The DNA vaccines of the present invention can be characterized as a novel form of "gene therapy" in that the vaccine must transfect antigen presenting cells (APC) in order to elicit an immune response. This is also a very unpredictable field. For *prima facie* obviousness, there must be a reasonable expectation of success that the proposed combination will work. This presupposes that the skilled person is capable of rationally predicting, on the basis of existing knowledge, the successful conclusion of the subject invention without undue experimentation. The more unexplored a technical field of research is, the more difficult it is to make predictions about the likelihood of success. The present rejection simply presupposes, without any basis in fact, too much knowledge and predictability on the part of the person of ordinary skill and the field of endeavor, in a manner which is wholly inconsistent with the Examiner's prior position *vis-a-vis* the alleged lack of

enablement of the prior claims, in which the unpredictability of the art was asserted.

In the present case, there are many potential choices for the tumor antigen and for the selection of a cytokine adjuvant, coupled with the need to select a delivery vehicle that will be effective for both the tumor antigen and the cytokine. The selection of all of these variants based on the applied art would clearly have involved undue experimentation. See also *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (no identification of a predictable solution where prior art discloses a broad selection of compounds).

The principal reference, Rovero *et al.*, discloses a plasmid DNA vaccine (not a bacterial vector) encoding the tumor antigen Her-2/neu (not survivin) and an immunologically active fragment of IL-1β (not CCL21). The reference reports that immunization with this vaccine elicited lymphocyte infiltration into the stroma surrounding the terminal ductal-lobular units (TDLU) and induction of antibodies against the Her-2/neu antigen (anti-p185neu), and delayed tumor appearance in mice, but did not induce significant cytotoxic T lymphocyte (CTL) response (see page 449, col. 2, last full paragraph). Rovero *et al.* also reported that a plasmid DNA encoding only the Her-2/neu antigen did not elicit any significant immune response in the same mouse model (*Id.*).

In contrast, the presently claimed vaccine does indeed elicit activation of CTLs (i.e., CD8 T cells). The present application indicates that while a vaccine encoding only the survivin protein did induce some anti-tumor response, the claimed combination encoding both survivin and CCL21 was significantly more effective (see in particular the results described in Examples 4, 5, and 17, on pages 33-35 and 44-45, demonstrating significant CD8 T cell activation in mice treated with the claimed vaccines, and Examples 3, 8, and 15, on pages 31-33, 36-37, and 41-43). These results show that the presently claimed vaccines indeed operate by a significantly different immunological mechanism, i.e., via cellular immunity (CTL activation). The vaccines of Rovero *et al.* on the other hand, appear to invoke only humoral immunity (antibody production), a different immunological mechanism.

The immune system is indeed complex and unpredictable. In order to be effective, immune system cells (e.g., B cells, Th cells, and/or CTLs) must migrate to, and infiltrate the tumor cite. Nagira *et al.*, while providing general statements about the utility of a particular antigen or cytokine, provide little more than an invitation to experiment, but do not

provide to one of ordinary skill a reasonable expectation that modifying a vaccine such as that of Rovero *et al.* by replacing the antigen target as well as the immunostimulating cytokine would be successful. This is particularly evident in the present case, where more than one factor is being altered in the primary reference at the same time, and the mechanism of the immune response is dramatically different.

Obviousness must be assessed on the claimed invention as a whole. *Stratoflex, Inc. v. Aeroquip Corp.*, 218 USPQ 871 (Fed. Cir. 1983); M.P.E.P. 2141.02. One of ordinary skill in the art would not have had a reasonable expectation that the numerous modifications of the Rovero vaccine required by the present rejection would have been successful. For one of ordinary skill in the art to develop the present invention would have required selection of survivin from a very large number of known tumor-associated antigens, followed by selection of CCL21 from a large number of adjuvants that can enhance immune response, and then also selecting an entirely different vector (i.e., the presently claimed *S. typhimurium* vector) to replace the plasmid of the Rovero vaccine. All of these selections being performed in an unpredictable art. Thus, many combinations of antigen, adjuvant and vector would have had to be constructed and tested in numerous tumor models to finally arrive at a successful end product. Such a scenario clearly involves the kind of undue experimentation that mitigates against a finding of obviousness. The prior art does not provide a predictable road-map to combine all of the elements of the present claims together without undue experimentation. The only road-map to the presently claimed invention of record here is the present application, itself. Hindsight use of the teachings of the application as a guide for combining all of the elements of the claims clearly is improper. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Unexpected Results.

Regardless of whether or not a *prima facie* case for obviousness has been established, the present invention provides benefits and results that are unexpected and could not have been predicted based on the teachings of the prior art. For example, the data in Table 2, on page 35, clearly demonstrate a significant upregulation of CD8 T-cells that express CD25, CD28 and CD69 activation markers, in comparison to examples involving only the survivin protein or only the CCL21. These increased expression levels would not have been

predictable from the allied prior art, i.e., Nagira *et al.*, which does not disclose or even suggest the enhanced expression of these T-cell markers by CCL21.

As a further example, the data in Table 3, on page 42, clearly indicates a dramatic reduction in D121 Lewis lung tumor metastasis in mice vaccinated with the claimed vaccine relative to mice treated with a vaccine comprising survivin DNA alone or CCL21 DNA alone, i.e., 6 out or 8 mice treated with the claimed virus had metastasis scores of "0", and the remaining mice had scores of "1", compared to the results from mice from the survivin or CCL21 treatment groups, in which the majority of mice had metastasis scores of "2" or "3". The prior art simply does not provide sufficient information for one of ordinary skill to have predicted these improvements demonstrated by the present invention. Accordingly, the obviousness rejection should not be maintained.

Conclusion.

In view of the foregoing, Applicants request reconsideration, allowance of the present claims, and early passage of the application to issue.

Respectfully submitted,

Dated 17 July 2008 By _____
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